

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES***

Applicant: H. William BOSCH et al.

Title: STERILE FILTERED NANOPARTICULATE FORMULATIONS
OF BUDESONIDE AND BECLOMETHASONE HAVING
TYLOXAPOL AS A SURFACE STABILIZER

Appl. No.: 10/035,324

Filing Date: 1/4/2002

Examiner: Mina Haghigian

Art Unit: 1616

Confirmation 2223
Number:

REPLY BRIEF

Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Under the provisions of 37 C.F.R § 41.39, this Reply Brief is submitted in response to the Examiner's Answer, dated November 24, 2009. Although Appellants believe that no fee is required, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

REAL PARTY IN INTEREST

The real party in interest in this appeal is Elan Pharma International, Ltd., which is the assignee of the present application as recorded at Reel/Frame numbers 012770/0890.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 8 and 12 are canceled.

Claims 1-7, 9-11, and 13-37 are pending in the application, with claims 15-34 withdrawn from consideration. The claims under examination and the withdrawn claims are related as product and process claims. Therefore, the withdrawn process claims are subject to a rejoinder upon allowance of the corresponding product claims.

Claims 1-7, 9-11, 13-14 and 35-37 are at least twice rejected, and are the subject of this appeal. The pending claims are presented in Appendix A of this Reply Brief.

STATUS OF AMENDMENTS

In the Office Action dated February 4, 2009, the Examiner indicated entry and consideration of an amendment filed October 29, 2008. No other claim amendments are pending in the application.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is to be argued in the reply brief. The relevant citation to the specification is shown in the parenthesis.

Independent claim 1 reads as follows:

1. A sterile, stable nanoparticulate dispersion {p. 1, l. 7; p. 9, l. 21} comprising:
 - (a) a liquid dispersion medium {p. 16, l. 28-p. 17, l. 1; p. 17, ll. 4-5};
 - (b) nanoparticulate beclomethasone particles, nanoparticulate budesonide particles, or a combination thereof dispersed in the dispersion medium, the nanoparticulate beclomethasone and nanoparticulate budesonide particles having an effective average particle size of less than 150 nm {p. 9, ll. 22-27; p. 11, ll. 13-15; p. 14, ll. 20-22, 27-29; p. 15, ll. 28-30; p. 16, l. 28-p. 17, l. 1; p. 17, ll. 4-5};
 - (c) tyloxapol as a surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles {p. 1, l. 6; p. 9, l. 23; p. 12, ll. 18-19}; and
 - (d) optionally, at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles {p. 9, ll. 24-25; p. 10, ll. 3-4; p. 11, ll. 13-14; p. 12 , ll. 29-30}, wherein the nanoparticulate dispersion is free from biological contaminants by sterile filtration with a filter having a pore size of 0.2 µm or less {p. 9, ll. 28-29; p. 20, l. 23; p. 21, ll. 12-13}.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first rejection to be reviewed on appeal is the rejection of claims 1-7, 9-11, 13-14 and 35-37 under 35 U.S.C. §103(a) over U.S. Patent No. 5,747,001 to Wiedmann et al. (“Wiedmann”) in view of U.S. Patent Application Publication No. 2007/0117862 by Desai et al. (“Desai”) and as evidenced by U.S. Patent No. 6,139,870 to Verrecchia (“Verrecchia”).

The second rejection to be reviewed on appeal is the rejection of claims 1-7, 9-11, 13-14 and 35-37 under 35 U.S.C. §103(a) over PCT Publication No. WO 96/25918 by Wood et al. (“Wood”) in view of Desai and as evidenced by Verrecchia.

ARGUMENT

Pursuant to the right under 37 C.F.R. § 41.39, Appellants take this opportunity to respond to certain comments set forth in the recently issued Examiner's Answer.

A. The cited references teach away from the claimed invention.

As discussed in the Appeal Brief filed on July 1, 2009, the claimed invention is based on the following unexpected findings: (i) that nanoparticulate active agents stabilized by surface stabilizers other than tyloxapol were unable to be sterile filtered; and (ii) that steroids other than budesonide and beclomethasone stabilized by tyloxapol were unable to be sterile filtered. *See* pages 15-17. The cited references do not teach or suggest the superior properties of the combination of beclomethasone/budesonide particles and tyloxapol as a surface stabilizer.

The Examiner's Answer continues to misinterpret the teachings of Desai. The Answer repeats the mantra that Desai is only used to show sterile filtration. What is missing with this statement is an investigation as to what is Desai sterile filtering – paclitaxel particles having human serum albumin as a surface stabilizer, which are distinguished from particles with “conventional” surface stabilizers.

Desai teaches *away* from the claimed invention by stating that the composition is prepared “in the absence of any conventional surfactants [such as tyloxapol]” (abstract, and page 5, paragraph [0050]). Desai achieves filterable nanoparticles by using proteins, e.g., human serum albumin (HSA), as a stabilizing agent (page 5, paragraph [0050]) and “by addition of a water soluble solvent to the organic phase and by carefully selecting the type of organic phase, the phase fraction and the drug concentration in the organic phase” (pages 5-6, paragraph [0051]).

B. Desai does not compensate for the deficiency of the primary references.

The Examiner maintains that Desai is only relied upon for its teaching of sterile filtration of dispersions and that the dispersions are taught by the primary references. *See* Examiner's Answer, page 10, lines 3-6.

The primary references, Wiedmann and Wood, do not teach a sterile filterable nanoparticulate composition comprising beclomethasone particles or budesonide particles, or a combination thereof. Instead, the primary references disclose a beclomethasone particle size in the range of $0.26 \mu\text{m} \pm 0.13 \mu\text{m}$ (*see* Wiedmann, column 12, lines 29-31; Wood, page 20, lines 26-27). As one skilled in the art would have understood, not all particles within this size range would be able to pass through a 0.22 micron filter. If Desai is only relied upon for the teaching of sterile filtration, then a gap between the combined teachings of the cited references and the claimed invention is left unfilled: how to obtain beclomethasone or budesonide particles that are able to pass through a 0.22 micron?

As discussed *supra*, Desai distinguishes itself from conventional methodology in the use of HSA to form a crosslinked polymeric shell. One skilled in the art would not have obtained the claimed composition stabilized by tyloxapol in view of the teaching of Desai, which employs HSA as a stabilizing agent.

Appellants note that Verrecchia is cited by the Examiner as additional evidence of sterile filtration, but is not relied on for the rejection. The Examiner fails to articulate how to obtain sterile filterable beclomethasone or budesonide particles in view of Verrecchia. Therefore, Verrecchia does not provide any support to the rejection rationale.

C. The Examiner improperly discounted the results presented in the specification in support of unpredictability.

As summarized in the appeal brief filed on July 1, 2009, the specification presents data showing that nanoparticulate active agent compositions stabilized by other surface stabilizers or

other steroids stabilized by tyloxapol could not be sterile filtered. The Examiner discounted the experimental data by asserting: (i) that the data “could be due to an error,” and (ii) that one out of eighteen examples “is equivalent to about 5%, which is not support for unpredictability. Examiner’s Answer, lines 3-6.

First, regarding point (i), MPEP 2145 requires that the Examiner should give proper weight to all evidence: “[c]onsideration of rebuttal evidence and arguments requires Office personnel to weigh the proffered evidence and arguments. Office personnel should avoid giving evidence no weight.” This rejection of Appellants’ data is the Examiner’s opinion and in contrast to established patent law.

Second, the data has more than one example in which that the nanoparticulate active agent composition could not pass through the 0.22 micron filter. For instance, Example 5 (budesonide stabilized by hydroxypropylmethyl cellulose having a particle size of 89 nm), Example 8 (budesonide stabilized by polysorbate 80 having a particle size of 192 nm), and Example 13 (beclomethasone stabilized by polysorbate 20 having a particle size of 193 nm) demonstrate that budesonide or beclomethasone particles stabilized by a surface stabilizer other than tyloxapol failed to pass through a 0.22 micron filter. Moreover, Example 15 (flunisolide stabilized by tyloxapol having a particle size of 99 nm), Example 16 (triamcinolone acetonide stabilized by tyloxapol having a particle size of 157 nm), Example 17 (triamcinolone acetonide stabilized by tyloxapol having a particle size of 144 nm), and Example 18 (triamcinolone acetonide stabilized by tyloxapol and polyvinyl pyrrolidone having a particle size of 117 nm) demonstrate that steroid particles other than budesonide and beclomethasone stabilized by tyloxapol failed to pass through a 0.22 micron filter.

To substantiate the rejection, the Examiner discounts the complexity of the claimed invention by boiling it down to its “gist” and “prescreen” the data to remove the unpredictability of obtaining a stable nanoparticulate budesonide or beclomethasone composition with the aid the impermissible hindsight.

Third, the percentage of the failing example is irrelevant to unpredictability. If one skilled in the art cannot reasonably predict which nanoparticulate active agent composition will successfully pass through a 0.22 micron filter before carrying out the experiment, then unpredictability is well supported by evidence on the record.

D. The teaching of “filtration” by the primary references would not have led one skilled in the art to “sterile filtration” step of the claimed invention and of the secondary reference.

The Examiner states that Wiedmann and Wood teach filtration but not sterile filtration. See Examiner’s Answer, page 4, last two lines; page 8, lines 3-4. The filtration process in Wiedmann and Wood cannot be equated with “sterile filtration”, nor can the disclosures of these references lead one skilled in the art to the sterile filtration of Desai and of the claimed invention. This is because filtration in the primary references is a process of sieving through a mesh screen to remove the grinding media from the particulate product (see Wiedmann, column 7, lines 18-22; Wood, page 12, first full paragraph); while sterile filtration is to remove living microorganisms from the final particulate product.

CONCLUSION

In view of the foregoing, reconsideration and reversal of the rejection of the claims is once again respectfully requested.

Respectfully submitted,

Date January 21, 2010

By Michelle Simkin, Reg. No. 34717

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Michele Simkin
Attorney for Appellants
Registration No. 34,717

APPENDIX A: CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A sterile, stable nanoparticulate dispersion comprising:
 - (a) a liquid dispersion medium;
 - (b) nanoparticulate beclomethasone particles, nanoparticulate budesonide particles, or a combination thereof dispersed in the dispersion medium, the nanoparticulate beclomethasone and nanoparticulate budesonide particles having an effective average particle size of less than 150 nm;
 - (c) tyloxapol as a surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles; and
 - (d) optionally, at least one secondary surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles, wherein the nanoparticulate dispersion is free from biological contaminants by sterile filtration with a filter having a pore size of 0.2 μ m or less.
2. (Previously Presented) The dispersion of claim 1, wherein the nanoparticulate beclomethasone particles, the nanoparticulate budesonide particles, or the combination thereof are present in an amount selected from the group consisting of about 99% to about 1% (w/w), about 90% to about 10% (w/w), about 80% to about 30%, and about 80% to about 40% (w/w), based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.
3. (Previously Presented) The dispersion of claim 1, wherein the concentration of tyloxapol is selected from the group consisting of from about 0.01 to about 90%, from about 1 to about 75%, from about 10 to about 60%, and from about 10 to about 30% by weight, based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.

4. (Previously Presented) The dispersion of claim 1, wherein the effective average particle size of the nanoparticulate beclomethasone particles, the nanoparticulate budesonide particles, or the combination thereof is less than 120 nm.

5. (Previously Presented) The dispersion of claim 1 wherein the effective average particle size of the nanoparticulate beclomethasone particles, the nanoparticulate budesonide particles, or the combination thereof is less than 100 nm.

6. (Previously Presented) The dispersion of claim 1 wherein the effective average particle size of the nanoparticulate beclomethasone particles, the nanoparticulate budesonide particles, or the combination thereof is less than 80 nm.

7. (Previously Presented) The dispersion of claim 1 wherein the effective average particle size of the nanoparticulate beclomethasone particles, the nanoparticulate budesonide particles, or the combination thereof is less than 50 nm.

8. (Cancelled)

9. (Previously Presented) The dispersion of claim 1, wherein the secondary surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, poloxamers, poloxamines, charged phospholipids, dioctylsulfosuccinate, Tetronic 1508®, dialkylesters of sodium sulfosuccinic acid,

sodium lauryl sulfates, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isobutylphenoxy poly-(glycidol), C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside, n-hexyl β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl β-D-thioglucopyranoside, and random copolymers of vinyl acetate and vinyl pyrrolidone.

10. (Previously Presented) The dispersion of claim 1, wherein the secondary surface stabilizer is selected from the group consisting of dioctylsulfosuccinate, sodium lauryl sulfate, hydroxypropylmethyl cellulose, benzalkonium chloride, and polyvinylpyrrolidine.

11. (Previously Presented) The dispersion of claim 1, wherein the nanoparticulate beclomethasone particles and/or the nanoparticulate budesonide particles are crystalline, semi-crystalline, or amorphous.

12. (Cancelled)

13. (Previously Presented) The dispersion of claim 1, wherein the nanoparticulate beclomethasone is in the chemical form of beclomethasone dipropionate.

14. (Previously Presented) The dispersion of claim 1 formulated into an aerosol for nasal or pulmonary administration.

15. (Withdrawn) A method of making a nanoparticulate composition comprising:

(a) dispersing particles of budesonide, beclomethasone, or a mixture thereof in a liquid dispersion medium; and

(b) applying mechanical means in the presence of grinding media to reduce the average particle size of budesonide, beclomethasone, or a mixture thereof in the liquid dispersion medium to less than about 150 nm, and

(c) sterile filtering the resulting nanoparticulate dispersion through a filter having a pore size of 0.2 µm or less rendering the dispersion free from biological contaminants; wherein tyloxapol is added to the liquid dispersion medium before or after milling, but before sterile filtering.

16. (Withdrawn) The method of claim 15, wherein the beclomethasone particles, budesonide particles, or a combination thereof are present in an amount selected from the group consisting of about 99% to about 1% (w/w), about 90% to about 10% (w/w), about 80% to about 30%, and about 80% to about 40% (w/w), based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.

17. (Withdrawn) The method of claim 15, wherein the concentration of tyloxapol is selected from the group consisting of from about 0.01 to about 90%, from about 1 to about 75%, from about 10 to about 60%, and from about 10 to about 30% by weight, based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.

18. (Withdrawn) The method of claim 15, wherein the effective average particle size of the beclomethasone particles, budesonide particles, or a combination thereof is selected from the group consisting of less than about 120 nm, less than about 100 nm, less than about 80 nm, and less than about 50 nm.

19. (Withdrawn) The method of claim 15 further comprising adding at least one secondary surface stabilizer to the liquid dispersion medium before or after milling.

20. (Withdrawn) The method of claim 19, wherein the secondary surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride,

calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, poloxamers, poloxamines, charged phospholipids, dioctylsulfosuccinate, Tetronic 1508®, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfates, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isonylphenoxy poly-(glycidol), C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside, n-hexyl β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl β-D-thioglucopyranoside, and random copolymers of vinyl acetate and vinyl pyrrolidone.

21. (Withdrawn) The method of claim 19, wherein the secondary surface stabilizer is selected from the group consisting of dioctylsulfosuccinate, sodium lauryl sulfate, hydroxypropylmethyl cellulose, benzalkonium chloride, and polyvinylpyrrolidine.

22. (Withdrawn) The method of claim 15, wherein the beclomethasone and/or budesonide particles are crystalline, semi-crystalline, or amorphous.

23. (Withdrawn) A method of making a nanoparticulate composition comprising:
(a) dissolving beclomethasone, budesonide, or a combination thereof in a solvent;

(b) adding the solubilized beclomethasone, budesonide, or a combination thereof to a solution comprising tyloxapol to form a clear solution;

(c) precipitating the solubilized beclomethasone, budesonide, or a combination thereof having tyloxapol adsorbed on the surface thereof using a non-solvent; and

(d) sterile filtering the resulting nanoparticulate dispersion through a filter having a pore size of 0.2 μm or less,

wherein the resulting composition of nanoparticulate beclomethasone, budesonide, or a combination thereof has an effective average particle size of less than about 150 nm.

24. (Withdrawn) The method of claim 23, wherein the beclomethasone particles, budesonide particles, or a combination thereof are present in an amount selected from the group consisting of about 99% to about 1% (w/w), about 90% to about 10% (w/w), about 80% to about 30%, and about 80% to about 40% (w/w), based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.

25. (Withdrawn) The method of claim 23, wherein the concentration of tyloxapol is selected from the group consisting of from about 0.01 to about 90%, from about 1 to about 75%, from about 10 to about 60%, and from about 10 to about 30% by weight, based on the total combined dry weight of beclomethasone, budesonide, and tyloxapol.

26. (Withdrawn) The method of claim 23, wherein the effective average particle size of the beclomethasone particles, budesonide particles, or a combination thereof is selected from the group consisting of less than about 120 nm, less than about 100 nm, less than about 80 nm, and less than about 50 nm.

27. (Withdrawn) The method of claim 23 further comprising adding at least one secondary surface stabilizer to the liquid dispersion medium before or after milling.

28. (Withdrawn) The method of claim 27, wherein the secondary surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides,

dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, poloxamers, poloxamines, charged phospholipids, dioctylsulfosuccinate, Tetronic 1508®, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfates, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isonylphenoxy poly-(glycidol), C₁₈H₃₇CH₂(CON(CH₃)-CH₂(CHOH)₄(CH₂OH)₂, decanoyl-N-methylglucamide, n-decyl β-D-glucopyranoside, n-decyl β-D-maltopyranoside, n-dodecyl β-D-glucopyranoside, n-dodecyl β-D-maltoside, heptanoyl-N-methylglucamide, n-heptyl-β-D-glucopyranoside, n-heptyl β-D-thioglucoside, n-hexyl β-D-glucopyranoside, nonanoyl-N-methylglucamide, n-noyl β-D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl-β-D-glucopyranoside, octyl β-D-thioglucopyranoside, and random copolymers of vinyl acetate and vinyl pyrrolidone.

29. (Withdrawn) The method of claim 27, wherein the secondary surface stabilizer is selected from the group consisting of dioctylsulfosuccinate, sodium lauryl sulfate, hydroxypropylmethyl cellulose, benzalkonium chloride, and polyvinylpyrrolidine.

30. (Withdrawn) The method of claim 23, wherein the beclomethasone and/or budesonide particles are crystalline, semi-crystalline, or amorphous.

31. (Withdrawn) A method of treating a patient in need with a nanoparticulate composition comprising administering to a patient in need a therapeutically effective amount of a

nanoparticulate composition of budesonide, beclomethasone, or a combination thereof, wherein said composition comprises:

- (a) budesonide, beclomethasone, or a combination thereof having an effective average particle size of less than about 150 nm; and
- (b) tyloxapol adsorbed on the surface of the budesonide and/or beclomethasone, wherein the nanoparticulate composition has been sterile filtered by passing through a filter having a pore size of 0.2 µm or less.

32. (Withdrawn) The method of claim 31, wherein said treatment is for an inflammatory disease.

33. (Withdrawn) The method of claim 31, wherein said treatment is for asthma, cystic fibrosis, or chronic obstructive pulmonary disease.

34. (Withdrawn) The method of claim 31, wherein said composition is administered via a nasal or pulmonary aerosol.

35. (Previously Presented) A sterile nanoparticulate dispersion consisting of:

- (a) nanoparticulate beclomethasone particles, nanoparticulate budesonide particles, or a combination thereof, the nanoparticulate beclomethasone and nanoparticulate budesonide particles having an effective average particle size of less than 150 nm; and
- (b) tyloxapol as a surface stabilizer adsorbed onto the surface of the nanoparticulate beclomethasone and/or the nanoparticulate budesonide particles in an amount effective to prevent the aggregation of the nanoparticulate beclomethasone and/or budesonide particles, wherein the sterile nanoparticulate dispersion is free from biological contaminants.

36. (Previously Presented) A sterile nanoparticulate dispersion produced by a process comprising the steps of:

- (a) dispersing particles of budesonide, beclomethasone, or a mixture thereof in a liquid dispersion medium; and

(b) applying mechanical means in the presence of grinding media to reduce the average particle size of budesonide, beclomethasone, or a mixture thereof in the liquid dispersion medium to less than 150 nm, and

(c) sterile filtering the resulting nanoparticulate dispersion through a filter having a pore size of 0.2 μm or less;

wherein the sterile nanoparticulate dispersion is free from biological contaminants, and wherein tyloxapol is added to the liquid dispersion medium before or after milling.

37. (Previously Presented) A sterile nanoparticulate dispersion produced by a process comprising the steps of:

(a) dissolving beclomethasone, budesonide, or a combination thereof in a solvent;

(b) adding the solubilized beclomethasone, budesonide, or a combination thereof to a solution comprising tyloxapol to form a clear solution;

(c) precipitating the solubilized beclomethasone, budesonide, or a combination thereof having tyloxapol adsorbed on the surface thereof using a non-solvent; and

(d) removing biological contaminants from the dispersion by sterile filtering the resulting nanoparticulate dispersion through a filter having a pore size of 0.2 μm or less,

wherein the resulting composition of nanoparticulate beclomethasone, budesonide, or a combination thereof has an effective average particle size of less than 150 nm.

APPENDIX B: RELATED PROCEEDINGS

No related proceedings are pending.